SEPTEMBER 1999
Volume 3, Issue 1

Cardiology Rounds

AS PRESENTED IN THE ROUNDS OF THE CARDIOVASCULAR DIVISION OF BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

Current perspectives in coronary intervention

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Over the past several years, there has been a profound evolution in the techniques used for percutaneous coronary intervention (PCI). Gruentzig first introduced balloon angioplasty in 1977 as an alternative to coronary bypass surgery in selected patients with focal lesions in proximal coronary vessels.[1,2] With improvements over the next decade in operator experience and equipment design, balloon angioplasty was subsequently extended to patients with multivessel coronary artery disease, reduced left ventricular function, and serious co-morbid medical conditions.[3]

By the late 1980s, it became apparent that there were at least two important limitations of conventional balloon angioplasty. Abrupt vessel closure resulting from dissection, thrombus, or both at the angioplasty site, occurred in 5% to 10% of patients, and emergency coronary bypass surgery was needed in 3% to 5% of patients due to angioplasty-induced ischemic complications.[4–6] The second major limitation was restenosis leading to symptom recurrence in 30% to 40% of patients within one year following the procedure.[7,8] In an effort to prevent the frequency of restenosis, numerous pharmacologic agents were tested, with only limited clinical success.[8,9]

New devices were introduced in the early 1990s to improve upon the outcomes achieved with conventional balloon angioplasty.[10,11] These devices were designed to remove (ie, directional, rotational, or extraction coronary atherectomy), to ablate (ie, excimer laser angioplasty), or to scaffold (ie, stents) atherosclerotic plaque. Randomized clinical trials comparing outcomes using these new devices with those from balloon angioplasty demonstrated that some devices (ie, stents)[12,13] resulted in better early and late clinical outcomes, while others (ie, excimer laser angioplasty)[14–16] imparted no incremental clinical benefit when applied broadly in patients with coronary disease. As some of the new angioplasty techniques were particularly useful in cases of complex or high-risk lesions,a lesion-specific approach to PCI was developed (table 1).[17]

This review will outline an evidence-based approach to PCI in patients with symptomatic atherosclerotic coronary artery disease. As we enter the "stents-plus" era, it is clear that further advances in PCI will involve the addition of basic science to the mechanical armamentarium,particularly relating to the management of patients with diabetes[18,19] and those with diffuse coronary disease. Angiogenesis and molecular approaches to plaque stabilization and the prevention of restenosis will also allow the treatment of more complex cases for whom conventional methods of surgical or percutaneous revascularization have, until now, not been an option.

Plain ol' balloon angioplasty

Balloon angioplasty exerts its beneficial effect on the coronary lumen by stretching and tearing the atherosclerotic plaque and vessel wall and, to a lesser extent, by redistributing plaque along the axial length of the vessel.[20–22] Although balloon dilatation is performed in virtually all cases of PCI, balloon angioplasty alone is limited by substantial early elastic recoil, resulting in an average 30% to 35% residual diameter stenosis. This is sufficient to relieve the majority of patients' ischemic symptoms, but, on occasion, propagation of a coronary dissection and superimposed platelet thrombus formation after balloon angioplasty result in early complications, including abrupt vessel closure.

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The editorial content of *Cardiology Rounds* is determined solely by the Cardiovascular Division of Brigham and Women's Hospital. This publication is made possible by an educational grant.

Table 1: A lesion-specific approach to coronary intervention

Technique	*Frequency	Indications
Stand-alone balloon angioplasty	15%	• small (<2.75 mm) vessels • long (>25 mm) lesions • saphenous vein graft (internal mammary) anastamotic sites • lesions at high risk for recurrence after stent placement
Directional atherectomy	5%	• bifurcation lesions • selected ostial lesions • restenotic stents in large (>3 mm) vessels
Rotational atherectomy	15%	• calcified lesions • long lesions in smaller vessels • undilatable lesions
Extraction atherectomy	<2%	• thrombus-containing saphenous vein grafts
Excimer laser angioplasty	<2%	• selected total occlusions • degenerated saphenous vein grafts • selected ostial saphenous vein graft lesions
Rheolytic thrombectomy	5%	• thrombus-containing native vessels and saphenous vein grafts
Coronary stents	65–75%	• focal (<25 mm) de novo or restenotic native vessel lesions • saphenous vein graft lesions • total occlusions • patients with acute MI • abrupt or threatened vessel closure

* Estimated;use of multiple techniques might result in frequency >100%.

When stent-like results (<20% residual stenosis) are achieved with balloon angioplasty, late-term outcomes are comparable to those achieved with coronary stents.[23] Documentation of such anatomic and physiologic results can be aided by Doppler flow studies and intravascular ultrasound.[24] In one study, a residual stenosis <35% and a Doppler coronary flow reserve ratio >2.5 was associated with a late clinical outcome identical to that from coronary stenting.[23] In clinical practice, however, stent-like results are infrequently (<25%) obtained with balloon angioplasty alone. Accordingly, "stand-alone" balloon angioplasty is now reserved for small (<2.75 mm) vessels, long (>25 mm) lesions, anastomotic stenoses in saphenous vein grafts, and other lesions deemed at high risk for stenting. In the event of a suboptimal result (>40% residual stenosis alone or in association with a coronary dissection), rescue stenting should be performed, reducing the need for emergency coronary bypass surgery to <1%.[25,26]

Directional coronary atherectomy

Directional coronary atherectomy was developed as an alternative to balloon angioplasty to focally excise atherosclerotic plaque from bulky, eccentric stenoses in native coronary vessels.[27] On average, 15 mg to 20 mg of macroscopic tissue can be removed using 5-7F directional atherectomy devices, most often resulting in a smooth lumen contour and very low (<20%) residual diameter stenoses.[28]

Two series that compared modest atherectomy with balloon angioplasty did not demonstrate a restenosis advantage from directional atherectomy.[29,30] BOAT (Balloon Versus Optimal Atherectomy Trial) was a randomized study of 1,000 patients with focal, de novo stenoses. It showed a reduction in angiographic restenosis from 39.8% after balloon angioplasty to 31.4% after directional atherectomy (P=0.016).[31] However, directional atherectomy is currently used in <10% of coronary interventional procedures, primarily due to the lower restenosis rates (<20%) for comparable lesion subsets achieved with coronary stents and the large (>9F) guiding catheters required for its use. Directional coronary atherectomy has maintained a niche, being generally reserved for bifurcation lesions,[32] ostial stenosis,[33] and for tissue removal from restenotic stent lesions in larger (>3 mm) vessels. A randomized trial (AMIGO) comparing late angiographic and clinical outcomes in patients undergoing directional atherectomy before stent placement or stent placement alone is currently under way.

Rotational coronary atherectomy

Rotational coronary atherectomy remains a useful adjunct method of coronary revascularization in patients with calcified or fibrotic atherosclerotic lesions.[34] Diamond chips embedded in the distal portions of 1.25 mm to 2.50 mm olive-shaped burrs rotating at 130,000 to 200,000 rpm are used to preferentially ablate rigid plaque, resulting in microparticulate (<5 micron) distal debris that appears to harmlessly pass through the distal microcirculation.

Rotational atherectomy in complex lesions has been shown to improve the procedural safety compared with balloon angioplasty.[14] Rotational atherectomy is preferentially used for calcified vessels, ostial lesions,[35] long lesions (particularly those in smaller vessels), and lesions that are not expandable using conventional balloon methods.[36] While rotational atherectomy enhances initial procedural safety in complex-lesion subsets, there appears to be little reduction in the frequency of late restenosis with this approach.[14] Rotational atherectomy has also been used before coronary stenting to improve the early procedural results.[37] A randomized trial, SPORT, comparing routine rotational atherectomy before stent implantation with primary stent implantation is in progress.

Thrombectomy devices

The presence of saphenous vein graft or native vessel coronary thrombus imparts a substantial risk of procedural complications, including distal embolization, no reflow, and non-Q-wave myocardial infarction (MI).[38] The Possis Angiojet is a 5F catheter that uses high-pressure saline jets to create a vortex suction at its distal tip to entrain thrombus into the catheter lumen.[39] The Angiojet rheolytic thrombectomy catheter has been shown to reduce the frequency of procedural complications compared with a prolonged (8-16 hours) urokinase infusion in patients with native-vessel or saphenous-vein-graft disease. A similar device using low-frequency ultrasound to sonicate thrombi in saphenous-vein grafts is currently under evaluation in the ATLAS trial.

Coronary stents

It is clear that the availability of coronary stents has dramatically changed the early and late clinical outcomes associated with PCI (table 2).[25,26] Their mechanism of benefit involves scaffolding coronary dissections and improving lumen dimensions. In the wake of two well-designed randomized

trials,[13,40] coronary stents became commercially available in 1994[11,41] and are now the preferred method of revascularization in patients with de novo[13,42] and restenosed[43] native vessel lesions, saphenous vein graft lesions,[12] and total coronary occlusions,[44] and in patients with acute MI.[45,46] It is now estimated that 60% to 80% of PCI procedures will include the use of one or more stents.

Although the Palmaz-Schatz balloon expandable stent has been the gold standard, several newer stent designs have improved the procedure's success rates.[47] The approval pathway for these stents has involved demonstrating their equivalency in late clinical outcome compared with the Palmaz-Schatz stent. Thus far, the Multilink (and DUET) stent, the Microstent II (and GFX), the NIR stent, the self-expanding Radius stent, and Wallstent have been approved for clinical use for the prevention of restenosis. A number of other stents will also soon be available.

Restenosis after PCI

Prior to the widespread use of intracoronary ultrasound, the primary mechanism of restenosis after balloon angioplasty and directional atherectomy was felt to be neointimal hyperplasia resulting from arterial trauma,[7] but serial intravascular ultrasound studies have since shown that the primary mechanism is arterial remodelling.[48–50] Although a plethora of agents have been tested to prevent restenosis after PCI, only two agents show promise in preliminary clinical studies. Probucol reduced restenosis after balloon angioplasty in a medium-sized randomized clinical trial, primarily by preventing arterial remodelling.[51] Tranilast, an antiallergic drug used widely in Japan, has been shown to reduce restenosis after successful directional coronary atherectomy.[52] Whether these agents prevent restenosis after coronary stent implantation will require further study.

A recent report of patients undergoing directional coronary atherectomy has suggested that cytomegalovirus (CMV) infection might play a role in restenosis after this procedure.[53] In a series of 75 consecutive patients undergoing directional coronary atherectomy for symptomatic coronary artery disease, angiographic restenosis was more frequent in seropositive patients (43%) than seronegative patients (8%) (P=0.002).[53] Whether anti-microbial agents will prevent restenosis after PCI is currently under investigation.

In contrast to the mechanism of restenosis in patients undergoing balloon angioplasty or directional atherectomy, restenosis after stent implantation is virtually all due to neointimal proliferation within the axial stent length.[54,55] Recurrence of symptoms can occur in 10% to 20% of patients within 12 months after stent implantation; after 6 to 12 months, it appears that contraction of the intimal tissue results in slightly larger lumen dimensions over time.[56]

Some patients with multivessel coronary artery disease or multiple stent restenoses who develop recurrent symptoms after stent placement are best served by coronary bypass surgery; however, the majority of patients with in-stent restenosis can be safely and effectively treated with repeat PCI.[57] Balloon angioplasty is the most commonly used method of repeat PCI in patients with stent restenosis.[58,59] The mechanism of benefit of balloon angioplasty relates to both expansion of the stent and extrusion of tissue through the stent struts and axially along its length.[60] Early (<40 minutes) tissue recoil might also account for "instant" restenosis in nearly 30% of patients.[61] After balloon angioplasty, rates of stent restenosis have ranged from 11% to 17%;[58,59] and higher recurrence rates prevail when the restenosis is diffuse (>15 mm) or severe (>70% diameter stenosis).[59]

Although atheroablation (directional, rotational, or excimer laser angioplasty) has been applied in patients at high risk for in-stent restenosis after PCI,[62] its advantage over conventional balloon angioplasty has not been demonstrated in randomized studies. For instance, a consecutive series of 60 patients with diffuse native-vessel in-stent restenosis was treated with either balloon angioplasty alone or balloon angioplasty plus debulking through rotational or directional atherectomy, and the immediate procedural success was 100% in both groups.[63] Despite longer lesion lengths in the debulking group (18.4 mm) compared with the balloon-alone group (13.5 mm) (P=0.09), treatment with atherectomy resulted in lower post-procedure stenoses (18%) compared with the balloon group (26%) (P=0.01). One-year repeat target-vessel revascularization was required in 28% of patients in the debulking group compared with 46% in the balloon-alone group (P=0.18). As a result of these pilot studies, debulking of in-stent restenoses appears to be most useful in patients with diffuse (>15 mm) stent restenosis.

Table 2: Randomized trials comparing the Palmaz-Schatz stent with balloon angioplasty

			Angiographic restenosis (%)			Major cardiac events (%) (TLR, %)		
Reference	**Lesion**	**N**	**Stent**	**Balloon**	**P value**	**Stent**	**Balloon**	**P value**
Fischman et al. *N Engl J Med* 1994;331:496	de novo native vessels	410	31.6	42.1	0.046	19.5 (10.2)	23.8 (15.4)	0.16 0.02
Serruys et al. *N Engl J Med* 1994;331:489	de novo native vessels	520	22	32	0.02	20	30	0.02
*Serruys et al. *Lancet* 1998;352:673	de novo native vessels	827	16	31	0.0008	12.8	19.3	0.013
Versaci et al. *N Engl J Med* 1997;336:817	proximal LAD	120	19	40	0.02	13	30	0.04
Erbel et al. *N Engl J Med* 1998;339:1672	restenotic lesions	383	18	32	0.03	16 (10)	28 (27)	0.04 0.001
Sirnes et al. *J Am Coll Cardiol* 1996;28:1444	total occlusion	119	32	74	<0.001	(22)	(42)	0.025
Savage et al. *N Engl J Med* 1998;337:740	SVGs	220	37	46	0.24	27	42	0.03

* heparin-coated Palmaz-Schatz stent
LAD = left anterior descending artery
SVG = saphenous vein graft
TLR = target lesion revascularization

An exciting avenue for the prevention of restenosis involves locally-delivered radiation after PCI. There are at least two generic approaches: gamma and beta radiation. In a randomized clinical trial of 55 patients at high risk for stent restenosis, gamma radiation from ^{192}Iridium significantly reduced the frequency of angiographic, ultrasound, and clinical restenoses.[64] Additional studies using other radiation sources to prevent de novo and stent restenosis are currently ongoing.

Platelet and glycoprotein IIb/IIIa (GP IIb/IIIa) receptor inhibitors

Until recently, the incidence of subacute thrombosis after coronary stent implantation ranged from 3% to 5%.[13,40] It is now clear that both mechanical factors (eg, inadequate stent deployment, unapposed stent struts, and margin dissection) and inadequate antiplatelet therapy contributed to the unacceptable rates of subacute thrombosis.

A recent randomized clinical trial of 1,650 patients undergoing successful stent implantation showed that the incidence of subacute thrombosis was significantly reduced in patients treated with the combination of ASA (acetylsalicylic acid) 325 mg + ticlopidine 250 mg twice daily (0.5% incidence) compared with ASA (325 mg) alone (3.6%), or ASA + warfarin (2.7%).[65] Because of the small but finite risk of ticlopidine-induced neutropenia and thrombotic thrombocytopenic purpura, clopidogrel (loading dose: 300 mg; maintenance dose: 75 mg daily for 30 days) may be used as an alternative to ticlopidine.[66]

A number of series has demonstrated the benefit of GP IIb/IIIa inhibitors on the reduction of clinical events early after PCI.[67] It is estimated that the inhibitors are used during 30% to 80% of PCI. Because routine use of GP IIb/IIIa inhibitors is costly, higher-risk patients are generally selected to receive these agents. Upstream use of the GP IIb/IIIa inhibitors tirofiban and eptifibatide in patients with unstable angina has also lessened ischemic complications in those undergoing PCI (see *Cardiology Rounds*, April 1998).

Early invasive strategies in ACS

Despite the improved procedural safety of PCI, identification of whether it should be performed and, if so, the optimal timing in patients presenting with acute coronary syndromes (ACS) has been controversial. Patients with ACS and one or more high-risk characteristics (ongoing resting pain, electrocardiographic changes, markers for myocardial necrosis, or provocable myocardial ischemia) might benefit from early angiography and coronary revascularization. The prognostic importance of routine angiography and revascularization in patients with ACS and no provocable ischemia, however, is less well established.

Randomized trials addressing early invasive or conservative approaches have yielded conflicting results. In the Thrombolysis In Myocardial Infarction (TIMI) IIIb study, the value of thrombolysis and the role of routine early coronary arteriography followed by revascularization was evaluated in 1,473 patients with unstable angina or non-Q-wave MI.[68] Patients were randomized to tPA (tissue plasminogen activator) or placebo as initial therapy. They were then assigned to early invasive treatment (coronary arteriography followed by revascularization when the anatomy was suitable) or to conservative treatment (coronary arteriography and revascularization if initial medical therapy failed). Six-week clinical outcomes (death, MI, or failure of initial therapy) were similar in the tPA and placebo groups. The end-point for comparison of the two intervention strategies (death, MI, or an unsatisfactory symptom-limited exercise stress test at 6 weeks) was also similar in patients assigned to the early invasive strategy (16.2%) and those assigned to the early conservative strategy (18.1%) (P = NS). However, the average length of initial hospitalization, incidence of rehospitalization within 6 weeks, and days of rehospitalization were significantly lower in patients assigned to the early invasive strategy in this pre-stent era study.[68]

The Veterans Affairs Non-Q-Wave Infarction Strategies In Hospital (VANQWISH) trial compared a routine early invasive strategy (angiography and revascularization) and a conservative, ischemia-guided approach in 920 patients with non-Q-wave MI.[69] Although the invasive strategy was associated with more frequent death or nonfatal MI within the hospitalization period, this was largely attributable to a high (11.6%) surgical mortality rate in those patients assigned to the invasive arm. During the mean 23-month follow-up period, there was no difference between the two groups in frequency of death or MI.

There are important limitations to both of these trials assessing the optimal approach to routine revascularization in patients with ACS. Neither study was performed in the era of stenting or with the availability of potent GP IIb/IIIa antagonists that have been shown to substantially reduce procedural complications in patients undergoing coronary intervention. It also appears that the timing of intervention was delayed compared with contemporary standards.

The TIMI-18 study is evaluating this approach in patients with ACS; they will receive ASA + heparin + tirofiban and will then be randomly assigned to an early invasive strategy (cardiac catheterization at 4 to 24 hours after presentation) or a conservative strategy that limits cardiac catheterization and revascularization to patients with recurrent or exercise-induced ischemia. Results of this study are anticipated within the next year.

Future directions

A number of clinical questions remain for interventional cardiologists as we approach the next millennium. Patients with insulin-dependent diabetes mellitus are a particular challenge for stent implantation, due to their diffuse coronary disease and enhanced neointimal proliferation.[18,19,70] Progression of coronary disease at remote sites is also more common in diabetic patients.[18] Aggressive risk factor modification, including glucose control and lipid reduction therapy, is warranted for these patients.[71]

Another challenge is patients with diffuse coronary disease that is not amenable to percutaneous[72] or surgical revascularization. These patients might benefit from therapies directed at arteriogenesis, or growth of new blood vessels, in the ischemic regions. A number of arteriogenic methods have been used, including laser therapy and growth factor (eg, vascular endothelial growth factor [VEGF] and fibroblast growth factor [FGF]) delivery.

These therapies will be the subject of intense evaluation over the next several years.

It is clear from intravascular ultrasound studies that coronary atherosclerosis is a ubiquitous process that presents with clinical manifestations only late in the disease process.[73] The ultimate therapy for coronary disease is its prevention by means of plaque stabilization prior to manifestation of unstable angina, MI, or sudden death.[71] Using catheter-based intravascular ultrasound to characterize vulnerable plaque might ultimately allow identification and treatment of plaques prone to rupture or progression before ischemic symptoms occur. Such developments would permit the interventionist both to fine-tune risk stratification beyond the extent of angiographic disease and, more importantly, deliver novel stabilizing therapies.

This is truly a rapidly-moving field that couples innovative devices with conventional systemic and local pharmacologic approaches to continue to improve on plain ol'balloon angioplasty.

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